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Daily oxytocin patterns in relation to psychopathy and childhood trauma in residential youth

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ABSTRACT

Inconsistent findings have been found on the relation between oxytocin levels and psychopathy or callous-unemotional (CU) traits in humans, potentially because the role of trauma in oxytocin secretion and the distinction between primary and secondary psychopathy have been overlooked so far. Primary psychopathy has a stronger biological background, whereas secondary psychopathy mainly develops due to environmental adversity, such as childhood trauma. This study investigated the interaction effects of CU traits and childhood trauma on daily salivary oxytocin levels in 57 males living in residential youth care facilities. Participants provided six saliva samples (morning, afternoon, and evening for two consecutive days) and completed self-report questionnaires on CU traits and childhood trauma. A mean daily oxytocin and an oxytocin pattern across the day were examined. A significant interaction between CU traits and one trauma category (emotional neglect) on mean daily oxytocin was observed, demonstrating that subjects with high CU traits and low levels of emotional neglect (primary psychopathy) exhibited lower daily oxytocin secretion compared to subjects with high CU traits and high levels of emotional neglect (secondary psychopathy). There were no significant interactions with the other trauma types or in daily oxytocin patterns. Our findings provided a first insight into the potentially distinct oxytocin concentrations in primary and secondary psychopathy, suggesting that primary psychopathy might be linked to lower daily oxytocin output. Future longitudinal studies are required to unravel the developmental patterns of oxytocin secretion and determine whether lower oxytocin output might be a biomarker of primary psychopathy.

1. Introduction

Oxytocin is a neuropeptide that has received much attention due its relation to social behaviors, such as social affiliation, pair bonding, emotion recognition, trust, empathy, altruism, and attachment (Campbell, 2008, 2010; Lee et al., 2009a; Veening and Olivier, 2013). Several approaches have been proposed to better understand the underlying mechanisms of oxytocin in social behaviors. Particularly, it has been suggested that oxytocin might play a role in the development of the social brain as it is involved in the processing of social sensory input in the neocortex during the first postnatal years (Vaidyanathan and Hammock, 2016). The neocortex is involved in more complex social and cognitive processing that is critical for the development of executive function and social cognition. A recent animal study found higher density of oxytocin receptors in association regions in the brain compared to primary sensory and motor regions and proposed that oxytocin might promote balance in inhibition and excitation in the association cortex that contributes to cortical plasticity and modulation of social behaviors (Duchemin et al., 2017). It has also been proposed that oxytocin modulates the salience of social stimuli in the environment by interacting with the dopamine's signal on salience coding and attention orientation (Shamay-Tsoory and Abu-Akel, 2016). Another approach argues that oxytocin is related to self-referential processing and interoception that might contribute to the development of empathy and promote in-group survival (Hurlemann and Scheele, 2016).

These approaches stem from extensive experimental research on the effects of oxytocin administration on a broad range of social-affective behaviors. Empirical evidence has revealed a positive effect on empathy, trust, emotion recognition, generosity, and altruism in humans (see for reviews Campbell, 2010; Lee et al., 2009a; Veening and Olivier,

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2013). Importantly, the effect of oxytocin administration is context-dependent (e.g., ingroup vs outgroup), increases attention to social stimuli, and is more pronounced in subjects with social-affective impairments (Bartz et al., 2011; Olff et al., 2013; Shamay-Tsoory and Abu-Akel, 2016; Zik and Roberts, 2015). In addition, evidence from genetic studies has supported an association between the oxytocin receptor gene (*OXTR*) and social behavior, pair bonding, social cognition, and social support, although the results were not universal (Bakermans-Kranenburg and Van Ijzendoorn, 2013; Ebstein et al., 2012). A series of experiments on mice showed that oxytocin release is increased in the ventral tegmental area during social interactions, which in turn increase the activity of dopamine neurons that play an important role in social reward, highlighting the role of oxytocin in prosocial behaviors (Hung et al., 2017). Based on this line of research, it has been argued that alterations in oxytocin concentrations may also be relevant in individuals with antisocial behavior or psychopathy who exhibit severe social-affective deficits (Fragkaki et al., 2017; Rice and Derish, 2015). Speculatively, lower oxytocin secretion might be associated with the affective deficits commonly observed in these individuals, such as lack of empathy and difficulties in social relationships. Limited oxytocin secretion at an early age might inhibit the development of a healthy social brain and contribute to the development of social-affective deficits. Nevertheless, it is still understudied whether endogenous oxytocin levels might be a biomarker of antisocial behavior or psychopathy.

Additional research has focused on the association between the *OXTR* gene and the development of antisocial behavior or psychopathy. Evidence from genetic studies in healthy and clinical populations have demonstrated a link between several *OXTR* polymorphisms and antisocial behavior (Hovey et al., 2015; LoParo et al., 2016; Malik et al., 2012; Smearman et al., 2015; Waller et al., 2016), conduct problems and callous-unemotional (CU) traits (Beitchman et al., 2012; Dadds et al., 2014a). CU traits are considered analogous to and a precursor of psychopathic traits in adulthood and they are defined as a range of affective and interpersonal characteristics, such as lack of guilt and shame, limited display of emotions, lack of empathy and use of others for personal gain (Frick et al., 2003, 2014; Frick and White, 2008). These characteristics correspond to Factor 1 of the two-factor Hare Psychopathy Checklist-Revised (PCL-R; Hare, 1991, 2003), the gold-standard measurement for psychopathy, which was later divided into separate “interpersonal” and “affective” components in the three- and four-factor models (Hare and Neumann, 2006). Moreover, *OXTR* methylation has been investigated in relation to CU traits and it was found that higher *OXTR* methylation was associated with higher CU traits and lower oxytocin plasma levels in adolescents with conduct problems (Dadds et al., 2014b). The authors argued that high methylation might indicate a down regulation of the oxytocin system. However, high methylation was related to CU traits only in adolescents and not in children, disputing a causal effect of methylation. It was rather suggested that CU traits lead to several behaviors, such as limited intimacy and eye contact with attachment figures, which lead to the down-regulation of the oxytocin system and consequently the increased methylation of *OXTR* that suppresses the expression of the gene (Dadds et al., 2014b).

Another study showed that male carriers of the A allele of rs1042778 had higher right amygdala reactivity in response to angry faces which was related to higher levels of antisocial behavior in a sample of 406 healthy young adults aged 18–22 years (Waller et al., 2016). A theoretical model supports the differential amygdala activation in psychopathy, arguing that central amygdala (CeA) is overactivated, whereas basolateral amygdala (BLA) is underactivated in psychopathy (Moul et al., 2012). Oxytocin might play a role in differential amygdala activation due to its inhibitory effect on the medial central amygdala. This inhibitory effect might be reduced when the levels of central oxytocin are low, leading to higher activity of central amygdala (Moul et al., 2012). Although this model encompasses a broad range of systems and functions involved in differential amygdala activation, it is important to note that oxytocin is a part of the model, highlighting its potential contribution to the development of psychopathy.

A limited number of studies have examined the link between antisocial behavior or psychopathy and oxytocin levels in humans, providing inconsistent findings (see for a review Fragkaki et al., 2017). Some studies found lower oxytocin levels in relation to aggressive behavior in adults (Lee et al., 2009b) as well as in children and adolescents with attention deficit hyperactivity disorder (ADHD) (Demirci et al., 2016; Sasaki et al., 2015), conduct disorder (CD), and CU traits (Levy et al., 2015). In contrast, one study found higher oxytocin levels in adult incarcerated psychopaths compared to healthy controls (Mitchell et al., 2013). However, these studies should be interpreted with caution as they included only one measurement of oxytocin per individual failing to reflect a robust diurnal rhythm and used different methods of assay (blood, saliva, urine) that are not reliably comparable (McCullough et al., 2013). It has been established that multiple measurements are required for reliable hormonal output due to fluctuations across the day as well as within and between-person differences (Segerstrom and Smith, 2012). It is thus imperative to investigate the daily pattern of oxytocin more thoroughly with multiple daily measurements to better understand the association between oxytocin secretion and antisocial behavior or psychopathy.

Crucially, to disentangle this association, it is of paramount importance to take into account the presence of previous traumatic experiences (Fragkaki et al., 2017). Trauma and early social deprivation can alter oxytocin synthesis and oxytocin receptor binding, which in turn might mediate the link between early negative experiences and social behaviors (Veenema, 2012). Additionally, a meta-analysis of 18 studies ($N = 675$) showed that oxytocin has an anxiolytic effect as it increases in response to stressful situations that stimulate the Hypothalamic-pituitary-adrenal (HPA) axis and leads to cortisol decrease in order to reduce stress in clinical populations (Cardoso et al., 2014). Evidence from human studies revealed abnormal (both higher and lower) oxytocin levels in individuals with a history of trauma, supporting a main effect of trauma on oxytocin secretion (Fragkaki et al., 2017; Zik and Roberts, 2015). It has also been proposed that timing of trauma plays a crucial role in oxytocin concentrations (Fragkaki et al., 2017). Based on oxytocin’s anxiolytic effects, current or recent trauma might lead to higher oxytocin levels to cope with the emotional distress, whereas past trauma might lead to neuroendocrine alterations in the long run (De Bellis and Zisk, 2014; McCrory et al., 2010) that might also be reflected in lower oxytocin concentrations (Fragkaki et al., 2017).

Despite the high prevalence rates of trauma in adolescents with antisocial behavior (Dierkhising et al., 2013; Fox et al., 2015), only one study examined the link between antisocial behavior, CU traits, and oxytocin in adolescents with trauma and revealed a negative association between oxytocin and conduct problems as well as CU traits (Levy et al., 2015). However, a comparison group of adolescents without trauma was not included in this study and it is obscure whether lower oxytocin was specifically related to antisocial behavior, CU traits, trauma, or their combination. Crucially, antisocial behavior and psychopathy or CU traits, although highly related, are distinct concepts with unique neuroendocrine, biological, cognitive, and emotional characteristics (Frick et al., 2014; Frick and White, 2008). For instance, CU traits in youth have been consistently linked to more severe affective deficits and neuroendocrine alterations (such as lower cortisol levels) compared to subjects with antisocial behavior (Frick et al., 2014; Frick and White, 2008). In addition, psychopathy is a complex construct with distinct subtypes. Specifically, although history of trauma is a risk factor for the development of psychopathy (Gao et al., 2010), not all psychopaths have a history of trauma. A pertinent important distinction has been proposed in the construct of psychopathy, namely primary and secondary psychopathy (Karpman, 1941; Poythress and Skeem, 2006).

Primary psychopathy refers to a spectrum of behavioral characteristics; interpersonal and affective deficits, such as lack of empathy and

conscience, shallow emotion, callousness, narcissism, deceitfulness, grandiosity, as well as difficulties in relationships, low anxiety, hypoactive behavioral inhibition system, and stronger genetic underpinnings (Poythress and Skeem, 2006). In contrast, secondary psychopathy, in addition to similar affective and interpersonal characteristics, is also characterized by emotion dysregulation, impulsivity, social withdrawal, hyperactive behavioral approach system, anxiety, depression, and negative emotionality (Poythress and Skeem, 2006). CU traits comprise the interpersonal and affective characteristics of both primary and secondary psychopathy and have been used as an indicator of these characteristics in youth. It is supported that secondary psychopathy is the outcome of adverse environment and traumatic experiences, as traumatized individuals develop emotional detachment and callousness to cope with the emotional distress (Karpman, 1941, 1946; Porter, 1996). Although emotional detachment is a normative coping mechanism to deal with trauma, this mechanism is crystallized in secondary psychopathy and turns into an emotionally blunted interpersonal style that further leads to antisocial and callous behavior (Kerig et al., 2012; Kerig and Becker, 2010; Poythress and Skeem, 2006). Porter (1996) supported that this emotional detachment and callousness are an acquired process in secondary psychopathy, whereas in primary psychopathy these traits are innate. Overall, primary psychopathy seems to have a stronger biological background whereas secondary psychopathy stems from environmental adversity.

Indeed, scientific evidence has confirmed these two distinct types of psychopathy in large samples across several countries in adulthood and youth (Drislane et al., 2014; Hicks et al., 2010; Kimonis et al., 2013; Skeem et al., 2007; Olver et al., 2015) and corroborated that subjects with primary psychopathy did not consistently have a history of trauma in contrast to subjects with secondary psychopathy who reported severe forms of maltreatment (Kimonis et al., 2012, 2017; Meehan et al., 2017). In addition, distinct neuroendocrine activity of cortisol and dehydroepiandrosterone (DHEA) has been found in primary and secondary psychopathy. A study in incarcerated adolescent boys found high DHEA in primary psychopathy but high afternoon cortisol-to-DHEA ratio in secondary psychopathy (Kimonis et al., 2017). Another study in undergraduate students reported lower cortisol levels in relation to primary psychopathic traits but higher cortisol levels in relation to secondary psychopathic traits (Vaillancourt and Sunderani, 2011). Moreover, a genetic study examined prospectively the association between *OXTR* methylation and primary and secondary psychopathy in youth (Cecil et al., 2014). The results showed that *OXTR* methylation at birth was related to higher CU traits in early adolescents exhibiting high CU traits but not internalizing problems (indicative of primary psychopathy). In contrast, *OXTR* methylation at birth was not related to CU traits in youth exhibiting high CU traits and internalizing problems (indicative of secondary psychopathy). Additionally, a high temporal stability of *OXTR* methylation was observed at age 9 in youth with primary psychopathy compared to youth with secondary psychopathy. This evidence has further contributed to our knowledge about distinct biological correlates in primary and secondary psychopathy.

It has been suggested that psychopathy might be related to lower oxytocin levels (Fragkaki et al., 2017), but specific oxytocin patterns in relation to primary and secondary psychopathy have yet to be examined. Based on the strong biological basis of primary psychopathy and its more severe affective deficits, it is possible that lower oxytocin secretion might be a biomarker of primary but not secondary psychopathy. Lower concentrations of oxytocin might be innate and contribute to the development of interpersonal and affective deficits that characterize primary psychopathy. However, the effect of trauma on oxytocin secretion and the unique link between secondary psychopathy and trauma further complicates this issue. Speculatively, subjects with secondary psychopathy might exhibit higher oxytocin due to their traumatic experiences and their effort to cope with the trauma. We hence argue that primary and secondary psychopathy might exhibit distinct oxytocin patterns that warrant further exploration to gain a better insight into the biological underpinnings of these two subtypes.

This study aimed to disentangle the daily oxytocin output in residential youth with various levels of CU traits and trauma to elucidate whether oxytocin concentrations differ in primary and secondary psychopathy. Importantly, we included three measurements of salivary oxytocin levels for two consecutive days in order to, first, obtain a more reliable overall daily oxytocin output and, second, to explore the oxytocin pattern across the day. Based on the distinction between primary and secondary psychopathy, the stronger biological background and severe affective deficits in primary psychopathy (Poythress and Skeem, 2006) and our hypothesis that primary psychopathy might be linked to lower oxytocin levels, we expected that adolescents with high CU traits but no history of trauma (indicative of primary psychopathy) would exhibit lower mean daily oxytocin concentrations compared to adolescents with high CU traits and a history of trauma (indicative of secondary psychopathy). In addition, due to the lack of evidence on daily oxytocin rhythm in psychopathic individuals, we also explored whether daily oxytocin patterns differ in primary and secondary psychopathy.

2. Method

2.1. Participants

This study recruited young males aged from 13 to 23 living in residential youth care facilities in the Netherlands. The participants were admitted to residential care for severe behavioral problems, mainly externalizing problems and delinquent behavior, and/or adverse family environment. All the boys who resided in groups for typical intelligence youth were approached for participation. Sixty-nine boys participated in the study; twelve boys did not provide more than one saliva sample or their oxytocin levels were undetectable in the saliva and were therefore excluded from all the analyses. The total number of participants was 57 with a mean age of 17.95 (SD = 2.44). The majority of the participants were of Dutch origin (82.5%). Data for a clinical diagnosis were available for 41 participants. Twenty-eight participants had a clinical diagnosis: ADHD/CD/oppositional defiant disorder (ODD) (n = 19), pervasive disorders (n = 5), depression (n = 3), posttraumatic-stress symptoms (n = 1), and four participants had more than one diagnosis. Approximately half of the participants followed a low level track in school (47.4%) and the other half followed a middle level track (49.2%). The length of staying in the facilities ranged from 2 months (15.8%) to 18 months (33.3%) and 63.2% of them had been admitted to another institution in the past.

2.2. Instruments

2.2.1. Callous-unemotional traits

Callous-unemotional traits were assessed with the Inventory of Callous-Unemotional traits – Youth version (ICU; Frick, 2003). It consists of 24 items rated on 4-point Likert scale (0 = *not at all true*, 3 = *definitely true*) and it has three subscales: callousness, uncaring, and unemotional. A total sum score is computed and higher scores indicate higher CU traits. The questionnaire includes statements such as “I seem cold and uncaring to others”. The ICU is widely used in samples of healthy adolescents, juvenile delinquents and offenders in several countries and it has good internal consistency, and good construct, convergent and discriminant validity (Essau et al., 2006; Fanti et al., 2013; Feilhauer et al., 2012; Kimonis et al., 2008, 2014; Roose et al., 2010). The Cronbach’s α in this study was 0.81.

2.2.2. Childhood trauma

Childhood traumatic experiences were assessed with the Childhood Trauma Questionnaire – Short Form (CTQ; Bernstein et al., 2003). It consists of 25 items about childhood traumatic experiences and has five subscales: physical, sexual, and emotional abuse, physical and

emotional neglect. The items are rated on a 5-point Likert scale indicating the frequency of the traumatic experiences (1 = *never true*, 5 = *very often true*). CTQ is a valid screening instrument for childhood trauma. A sum score of the items is calculated for each subscale separately and higher scores indicate higher frequency of childhood trauma. CTQ has good discriminant and construct validity (Thombs et al., 2009), high internal consistency in community and psychiatric populations (Cronbach's α = 0.84–0.95) and in street youth (Cronbach's α = 0.65–0.95) (Forde et al., 2012). Particularly, in Dutch samples Cronbach's α range from 0.63 to .95, and it is excellent in prison samples (Cronbach's α = 0.93) (Cima et al., 2008). The Cronbach's α in this study was 0.90 for physical abuse, .84 for sexual abuse, .89 for emotional abuse, 0.56 for physical neglect, and 0.89 for emotional neglect.

2.2.3. Oxytocin levels

Saliva samples were collected in tubes (5 ml) to measure oxytocin levels at three time points (morning, 10.00 a.m.; afternoon, 14.00 p.m.; evening, 17.00 p.m.) across two consecutive days. Participants were instructed not to eat, drink (except water), and smoke 1 h before the study. Samples were stored at −40 °C until analysis and analyzed at the Laboratory of Radboud University Medical Center. The concentration (pg/ml) of oxytocin was measured using a commercially available oxytocin ELISA kit (Enzo Life Sciences) using optical density (OD) as a readout measurement. Measurements were performed in duplicate. As controls, blank wells were measured. Total activity (TA) was calculated in the samples taking into account non-specific binding (NSB) and TA from B_0 wells. A standard curve of the OD resulting from a series of seven known oxytocin concentrations (15.6, 31.2, 62.5, 125, 250, 500 and 1000 pg/ml) was run for each plate. The observed intra-assay coefficient was 7.3% and the inter-assay coefficient was 9.4%. Intra-essay coefficients less than 10 and inter-assay coefficients less than 15 are considered acceptable. A daily average (mean) and an average morning, afternoon, and evening (pattern) oxytocin level were computed from the two sampling days based on each time point. On average, participants provided 5.2 of the 6 samples. The missing or undetectable values of oxytocin were 13% (n = 44) of the total number of samples (N = 342) across the two days.

2.3. Procedure

The present study was conducted at residential youth care facilities. Participants completed the ICU and CTQ and provided a maximum of six saliva samples in two consecutive days. Participation was completely voluntary and the participants were allowed to terminate their participation at any time. Written informed consent was obtained from all participants. Participants received a voucher of 15 euro as compensation for their participation after completing the questionnaires and providing the saliva samples. The study has been approved by the Ethical Committee of Maastricht University.

2.4. Analytic strategy

Preliminary analyses were performed to examine normality of the variables and missing data. We calculated a daily average (mean) and an average morning, afternoon, and evening (pattern) oxytocin level from the two sampling days for each time point (see for a similar methodology Fairchild et al., 2008; Vaillancourt and Sunderani, 2011) and checked the data for outliers. Values above 2 standard deviations (n = 15) were replaced by the value corresponding to 2 standard deviations above the mean. Values below 2 standard deviations were not observed.

First, we ran random coefficient regression analyses to examine the effect of trauma (physical/sexual/emotional abuse, physical/emotional neglect), CU traits, and their interaction on the mean oxytocin level. Second, we estimated the pattern of oxytocin levels across the day with latent growth curve models (LGM), using Mplus version 7.0 (Muthén and Muthén, 1998). The growth curves were estimated by the intercept (the initial oxytocin level in the morning) and the linear slope (the change in oxytocin levels across the day). Maximum likelihood estimation with robust standard errors was selected to handle non-normality and missing data. To estimate the fit of the models, we used the following fit indices: the root mean square error of approximation (RMSEA), the standardized root mean square residual (SRMR), the comparative fit index (CFI), and the Tucker-Lewis fit index (TLI). Values below 0.10 for RMSEA and SRMR, and above 0.90 for CFI and TLI are indicative of an acceptable fit (Browne et al., 1993; Byrne, 1998; MacCallum et al., 1996). However, more strict cut-off values of < 0.06 for RMSEA, < 0.08 for SRMR, and > 0.95 for CFI and TFI have also been proposed for a good fit (Hu and Bentler, 1999). We ran an unconditional model without predictors to examine the daily oxytocin pattern and then added CU traits, trauma types, and the interactions between CU traits and trauma types to examine their effect on oxytocin patterns. In all analyses we controlled for age due to the significant hormonal changes occurring across adolescence (Gunnar and Vazquez, 2015). We applied the False Discovery Rate (FDR) correction for multiple testing as we ran models for each trauma type separately (Benjamini and Hochberg, 1995).

3. Results

The oxytocin levels (pg/ml) were as follows: morning (M = 70.50, SE = 6.95), afternoon (M = 70.57, SE = 6.91), evening (M = 67.47, SE = 6.44), and daily output (M = 69.52, SE = 5.44). Table 1 presents the means and standard deviations of CU traits and trauma types, and Table 2 shows the correlations among all the variables. First, we examined whether the mean daily oxytocin was predicted by CU traits, trauma, and their interactions controlling for age. The mean daily oxytocin and the five trauma types were significantly positively skewed and therefore log transformed for the regression analyses. CU traits were not a significant predictor of mean daily oxytocin, b = -0.003, p = .563. A significant CU traits x emotional neglect interaction was observed, b = 0.048, p = .005. After the FDR correction, the interaction remained significant with an adjusted p value of .025. A simple slope analysis was performed to interpret the interaction, using values corresponding to +1 *SD* above the mean and -1 *SD* below the mean of CU traits and emotional neglect. The results showed that subjects with high CU traits and low emotional neglect exhibited lower mean daily oxytocin compared to subjects with high CU traits and high emotional neglect, simple slope = -0.015, p = .037 (see Fig. 1). None of the other interactions with trauma types was significant (all ps > .05). Table 3 shows the results of all the multiple regression analyses.

Second, we ran latent growth models to examine the daily pattern of oxytocin. All models showed adequate fit and a linear slope was fitted to the data (see Table 4 for the model fit indices). The linear unconditional model for oxytocin levels yielded a non-significant effect of slope, b = -1.848, p = .639, suggesting a stable trajectory of oxytocin across the day. The variance of the intercept was significant, var = 1744.27, p = .023, whereas the variance of the slope was not significant, var = 286.45, p = .323, indicating the presence of individual differences in morning oxytocin levels but not in the change of oxytocin

Table 1
Means and standard deviations of CU traits and trauma types.

	M	*SD*	Range
Callous-Unemotional traits	29.95	9.98	11 – 61
Physical abuse	8.75	5.28	5 – 23
Sexual abuse	6.37	3.14	5 – 20
Emotional abuse	9.02	5.04	5 – 25
Physical neglect	9.60	3.78	5 – 19
Emotional neglect	12.30	5.87	5 – 25

Table 2
Correlations among all study variables.

	1	2	3	4	5	6	7	8	9	10
1. CU traits	–									
2. Physical abuse	−.249	–								
3. Sexual abuse	−.101	.646**	–							
4. Emotional abuse	−.264*	.789**	.594**							
5. Physical neglect	−.045	.499**	.330*	.562**	–					
6. Emotional neglect	.135	.461**	.332*	.577**	.686**	–				
7. Oxytocin morning	−.041	.113	.003	.209	.216	.317*	–			
8. Oxytocin afternoon	.068	−.073	−.061	−.045	−.003	.069	.529**	–		
9. Oxytocin evening	−.126	−.072	−.078	−.063	−.028	−.044	.461**	.457**	–	
10.Oxytocin daily	−.038	−.013	−.055	.042	.078	.143	.822**	.824**	.781**	–

Note. CU traits = callous-unemotional traits.
* $p < .05$, ** $p < .01$.

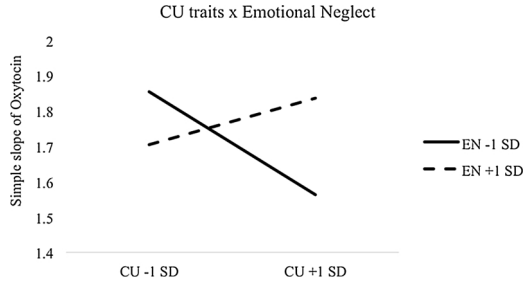

Fig. 1. Simple slope analysis for the interaction between callous-unemotional (CU) traits and Trauma category (emotional neglect; EN) on mean daily oxytocin for 1 standard deviation above (+1 SD) and below (-1 SD) the mean for CU traits and emotional neglect.

Table 3
Results of multiple regression analyses for mean daily oxytocin.

	b	*SE*	*t*	*p*
CU traits	−0.003	0.004	−0.579	.563
Physical abuse	0.078	0.173	0.450	.652
CU traits * Physical abuse	0.013	0.019	0.704	.481
Sexual abuse	0.013	0.201	0.066	.948
CU traits * Sexual abuse	0.008	0.016	0.510	.610
Emotional abuse	0.270	0.234	1.157	.247
CU traits * Emotional abuse	0.036	0.030	1.205	.228
Physical neglect	0.141	0.187	0.755	.450
CU traits * Physical neglect	0.016	0.022	0.724	.469
Emotional neglect	0.139	0.174	0.796	.426
CU traits * Emotional neglect	0.048	0.017	2.824	**.005**

Note. CU traits = callous-unemotional traits.

Table 4
Model fit indices for the latent growth models.

	Model fit indices					
	χ^2	df	*RMSEA*	*CFI*	*TLI*	*SRMR*
Oxytocin – Age, CU traits	4.831	5	0	1	1.016	0.048
Oxytocin – Age, CU traits, PA	4.330	5	0	1	1.121	0.031
Oxytocin – Age, CU traits, SA	4.183	5	0	1	1.119	0.028
Oxytocin – Age, CU traits, EA	3.945	5	0	1	1.158	0.033
Oxytocin – Age, CU traits, PN	3.018	5	0	1	1.281	0.029
Oxytocin – Age, CU traits, EN	3.598	7	0	1	1.292	0.039

Note. RMSEA = root mean square error of approximation; CFI = comparative fit index; TLI = Tucker-Lewis fit index; SRMR = standardized root mean square residual; CU traits = callous-unemotional traits; PA = physical abuse; SA = sexual abuse; EA = emotional abuse; PN = physical neglect; EN = emotional neglect.

Table 5
Parameter estimates for latent growth models.

	Intercept			Slope		
	Estimate	SE	*p*	Estimate	SE	*p*
CU	0.298	0.740	.688	−0.404	0.404	.317
PA	0.580	1.298	.655	−0.603	0.878	. 492
CU * PA	−0.094	0.156	.546	0.092	0.086	.287
SA	−0.288	1.285	.823	−0.507	0.978	.604
CU * SA	0.011	0.104	.916	0.019	0.051	.716
EA	1.370	2.004	.494	−0.313	1.065	.769
CU * EA	−0.113	0.258	.661	0.225	0.143	.116
PN	3.631	1.838	**.048**	−1.994	0.987	**.043**
CU * PN	0.110	0.238	.645	0.094	0.122	.444
EN	2.820	1.224	**.021**	−1.895	0.712	**.008**
CU * EN	0.171	0.128	.181	0.054	0.075	.467

Note. CU traits = callous-unemotional traits; PA = physical abuse; SA = sexual abuse; EA = emotional abuse; PN = physical neglect; EN = emotional neglect.

levels across the day. We then added age and CU traits in the model. Age did not have a significant effect on the intercept, $b = 4.754$, $p = .159$, or the slope, $b = -2.096$, $p = .162$. CU traits had no significant main effect on the intercept, $b = 0.298$, $p = .688$, or the slope of oxytocin, $b = -0.404$, $p = .317$.

Next, we added each trauma type and CU traits x trauma type interactions in separate models and found no significant effect of any interaction on oxytocin patterns across the day. Table 5 presents all the parameter estimates of the latent growth models. A significant main effect of emotional neglect on the intercept ($p = .021$) and the slope ($p = .008$) was observed, as well as a significant main effect of physical neglect on the intercept ($p = .048$) and the slope ($p = .043$). Participants with higher levels of physical and emotional neglect exhibited higher morning oxytocin that decreased across the day compared to participants with lower levels of physical and emotional neglect. After FDR correction, the effect of emotional neglect on the slope was trending (adjusted $p = .08$) and the effect of emotional neglect on the intercept as well the effect of physical neglect on the intercept and slope were no longer significant (adjusted $p > .10$).

4. Discussion

This study was the first investigation of daily oxytocin concentrations in relation to characteristics of primary and secondary psychopathy in residential youth. First, oxytocin had a stable trajectory across the day and individual differences were observed in morning oxytocin levels but not in the overall pattern of change throughout the day. The findings also revealed that CU traits interacted with emotional neglect, demonstrating that subjects with high CU traits and low emotional neglect had lower levels of mean daily oxytocin compared to subjects with high CU traits and high levels of emotional neglect.

Our study provided the first evidence of distinct oxytocin output in primary and secondary psychopathy. Subjects with high CU traits and low levels of emotional neglect (indicative of primary psychopathy) exhibited lower oxytocin output compared to subjects with high CU traits and high emotional neglect (indicative of secondary psychopathy). This finding supports our hypothesis that primary psychopathy might be characterized by lower oxytocin concentrations compared to secondary psychopathy. Primary psychopathy is characterized by more severe affective deficits and biological underpinnings, whereas secondary psychopathy is related to emotional problems and stems from adverse experiences (Karpman, 1941; Poythress and Skeem, 2006). Limited previous evidence also supported a negative association between CU traits and oxytocin levels in adolescents (Levy et al., 2015), but did not take into account the role of trauma and the distinction between primary and secondary psychopathy. Our findings showed that low oxytocin output might be especially related to primary psychopathy as indicated by high CU traits in combination with low trauma, contributing to the evidence supporting a stronger biological background of primary psychopathy.

Given the role of oxytocin in the development of the social brain and the processing of social information (Hurlemann and Scheele, 2016; Shamay-Tsoory and Abu-Akel, 2016; Vaidyanathan and Hammock, 2016), it is possible that the lower oxytocin levels observed in subjects with primary psychopathy may partially inhibit the successful development of the social brain and the modulation of successful social behaviors, which may lead to social-affective deficits. If oxytocin expression in the brain is limited at an early age, it might impede the processing of social stimuli and the development of cortical plasticity that contributes to the formation of social-affective behaviors and social relationships, which in turn might lead to the development of primary psychopathy. Conversely, in secondary psychopathy oxytocin expression might be intact and these fundamental processes might have been successfully developed, but the psychopathic traits are expressed as a coping mechanism to deal with emotional distress. However, this interpretation cannot be substantiated by our cross-sectional findings, but future studies measuring oxytocin secretion at an early age could gain insight into the development of the oxytocin system.

Interestingly, the interaction between CU traits and trauma was found only for emotional neglect and not for the other trauma types. Emotional neglect refers to an adverse family environment, which is inadequate to satisfy the child's psychological and emotional needs. Neglectful parents exhibit limited and insufficient parent-child interactions, emotional support, and affective exchange, which could lead to affective deficits in their children. This emotionally neglectful and cold family environment can lead to the development of psychopathy and especially CU traits that are predominantly characterized by affective deficits (McCord and McCord, 1956). Relatedly, cumulative evidence has shown that insecure attachment style and emotionally detached parent-child relationship were associated with psychopathy (Bailey and Shelton, 2014). Therefore, emotional neglect seems to play a crucial role in the development of CU traits and especially secondary psychopathy that can make the distinction between the two variants as well as the distinct oxytocin patterns more clear. In line with previous findings, adverse environment might contribute to secondary psychopathy, whereas biological factors might be more relevant for primary psychopathy. Nevertheless, secondary psychopathy is related to several forms of maltreatment (Kimonis et al., 2012; Meehan et al., 2017) and evidence of emotional neglect in primary psychopathy has also been found (Kimonis et al., 2013). In this study, we measured five specific trauma types, but there are other traumatic experiences often observed in this population (e.g., incarceration or illicit drug use of parents) that might also be related to secondary psychopathy. Considering that trauma severity in our study was low to moderate for all trauma types and focused on childhood trauma, it is imperative to further investigate whether higher levels of childhood trauma or other traumatic experiences might reveal similar interactions between CU traits and trauma in oxytocin concentrations.

Importantly, we argue that low oxytocin levels in adolescents with high CU traits and low levels of trauma might serve as an indicator of further development of primary psychopathy in adulthood. Future research may benefit from longitudinal studies examining oxytocin concentrations from childhood to adolescence and adulthood to establish whether low oxytocin levels are indeed associated with the development of primary psychopathy. If that were the case, it would be useful to use oxytocin output as an early indicator of primary psychopathy to, first, distinguish the two types of psychopathy in youth and, second, provide tailored interventions better suited for each type. As suggested by Kimonis et al. (2017), interventions targeting emotional deficits may be more beneficial for primary psychopaths, whereas cognitive-behavioral interventions focusing on internalizing problems, emotional regulation, and coping skills for dealing with trauma might be more appropriate for secondary psychopaths.

We also found marginal effects (after correction for multiple testing) of physical and emotional neglect on daily oxytocin patterns. Subjects with high levels of physical or emotional neglect exhibited higher oxytocin levels in the morning that decreased across the day compared to subjects with low levels of physical or emotional neglect who exhibited a flatter diurnal rhythm. These findings are in line with previous evidence supporting a link between trauma and abnormal oxytocin concentrations (Fragkaki et al., 2017; Veenema, 2012; Zik and Roberts, 2015) and provide the first direction for the effect of trauma on diurnal oxytocin patterns in residential youth. It has been argued that current or recent traumatic experiences might lead to higher oxytocin levels to deal with the emotional distress, whereas past traumatic experiences might result in neuroendocrine alterations and lower oxytocin secretion in the long run (Fragkaki et al., 2017). In our study, the traumatized participants were adolescents recently placed out of their homes, where they were living in an adverse family environment. They have to adapt to the life in the institutions and simultaneously deal with their previous traumatic experiences, supporting the theory that recent or current trauma might lead to higher oxytocin concentrations. Moreover, early trauma affects oxytocin synthesis and oxytocin receptor binding, which might have long-term effects on the oxytocin system (Veenema et al., 2012). Crucially, these trending effects should be interpreted with caution and can be more useful as a direction for future research on the effects of trauma on diurnal oxytocin patterns in residential youth.

In addition, these findings were specific to physical and emotional neglect, suggesting that the effect of trauma on oxytocin secretion might be specific to these trauma types. The concept of childhood trauma includes a broad range of diverse forms of traumatic experiences that might have distinct effects on neural development (McLauglhin et al., 2014). A recent conceptual framework posits the importance of differentiating between deprivation and threat in childhood adversity as these two dimensions might have unique effects on neurodevelopment and behavior (McLauglhin et al., 2014). Relatedly, different types of trauma might lead to distinct physiological and neurobiological responses that might affect the brain and the regulation of the HPA axis differently in the long run (Kuhlman et al., 2015; Miller et al., 2007). Consequently, different trauma types might also influence oxytocin secretion in a distinct way. However, our sample consisted of adolescents with low to moderate levels of trauma according to the cut-offs of the CTQ Manual (Bernstein and Fink, 1998). It is thus possible that higher levels of other trauma types might also have an effect on oxytocin output, pointing to a need for future research on populations with higher levels of trauma to draw more solid conclusions.

Lastly, we observed a flat diurnal rhythm of oxytocin in residential youth. Unfortunately, typical developmental patterns of oxytocin are understudied and limited evidence on oxytocin levels across the day has yielded lower oxytocin levels at late afternoon and higher at midnight in a small sample of 24 healthy males (Forsling et al., 1998). In addition, it is unknown whether oxytocin follows a different pattern in childhood, adolescence, and adulthood. More importantly, our study

included residential youth who often exhibit a broad range of psychopathology. Consequently, it is unknown whether a flat diurnal rhythm is characteristic of residential youth stemming from a diverse spectrum of social and emotional deficits or whether it is typical in adolescence. Further research on developmental patterns of oxytocin across the lifespan is crucial to determine the typical diurnal rhythm at each developmental stage in order to move toward a comprehensive understanding of alterations in diurnal patterns.

There are several limitations that should be acknowledged to better understand the generalizability of our findings. First, we used only CU traits and history of trauma as indicators of primary and secondary psychopathy, whereas these two variants include a range of distinct emotional and behavioral characteristics. For instance, apart from trauma history, anxiety is another characteristic of secondary psychopathy that is commonly used as a diagnostic identifier. However, the presence of trauma is one of the fundamental characteristics of secondary psychopathy and the lack thereof is central in primary psychopathy. Second, we used a self-report instrument to document history of trauma that, although it is widely used in research and has good psychometric properties, it still suffers from the known shortcomings of self-reporting and might underestimate trauma history especially in youth with primary psychopathy that might be less credible in self-reporting (Kahn et al., 2013). However, a study examined the variants of psychopathy using multiple informants and official records and found that secondary psychopathy was indeed associated with high levels of abuse based not only on retrospective reports but also on official records and there was no evidence of underreporting in relation to primary psychopathy (Kahn et al., 2013). Third, our sample size was not large enough to conduct a latent class analysis and identify two distinct groups corresponding to primary and secondary psychopathy, but we rather used CU traits and trauma as continuous variables. It is essential to corroborate this finding in larger samples with more clearly distinct groups of primary and secondary psychopaths. Fourth, our study was focused on residential youth, as this was an appropriate population to examine our research hypotheses due to high levels of CU traits and trauma usually observed in this population. Consequently, our findings cannot be generalized in community samples or other developmental periods. It is also important to mention that we did not acquire information about drug use or medication and it would be interesting in future research to examine whether they have an effect on oxytocin secretion. Relatedly, our sample included only males, but considering the sex differences in oxytocin concentrations (Lee et al., 2009a), it is essential to investigate these research hypotheses in females. Fifth, we used salivary measurements to assess oxytocin levels, but there are also other methods of assay, such as blood and urine samples. These different methods do not highly correlate with each other, rendering a comparison between them unreliable and there is still doubt about the reliability of salivary oxytocin (McCullough et al., 2013). However, blood or urine samples would be especially problematic in this study, as this specific population and the residential youth care facilities would be reluctant to participate if blood or urine samples were required. Finally, the cross-sectional design of our study does not allow us to explore the causal relation between trauma, CU traits, and abnormal oxytocin patterns as well as the consistency across development. Future research would thus benefit from longitudinal studies examining oxytocin patterns across the life span not only to unravel causal relations but also to establish whether low oxytocin is a biomarker of primary psychopathy.

Overall, our study was the first to examine the daily oxytocin concentrations in primary and secondary psychopathy in residential youth. It was revealed that CU traits interacted with emotional neglect on daily oxytocin output. Specifically, subjects with high CU traits and low emotional neglect (primary psychopathy) exhibited lower daily oxytocin compared to subjects with high CU traits and high emotional neglect (secondary psychopathy). Our study was a first step toward a deeper understanding of the neuroendocrine activity of oxytocin and the potentially distinct oxytocin patterns in primary and secondary psychopathy that should be further explored in larger longitudinal studies. A potentially distinct oxytocin output in primary and secondary psychopathy might serve as a biomarker and become a useful tool in the application of tailored interventions.

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Conflict of interest

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